Case Report

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TANAFFOS

Malignant Large Cell Calcifying Sertoli Cell Tumor of Testis with Skip Metastasis to Lung Presented With Peutz-Jeghers Syndrome

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Large cell calcifying Sertoli cell tumor of the testis (LCCSCT) is a rare tumor that is usually benign and multifocal. It may be associated with hereditary endocrine anomalies such as Carney's and Peutz-Jeghers syndromes. It is a rare histological variant of sex cord stromal tumors. It is exceptional in elderly men and the outcome is rarely fatal. We report a case of LCCSCT in a 44 year-old man with fatal outcome. The tumor involved the right testis and several areas of the tunica albuginea were grossly invaded. It composed of cords and trabeculae of large polygonal cells embedded in a myxoid and fibrous stroma with areas of calcification along with nuclear atypia, necrosis, and abundant mitoses. The Peutz-Jeghers syndrome (PJS) is known to be commonly associated with ovarian tumors. However, its association with testicular tumors is uncommon. To the best of our knowledge, this is the eight such case being reported in the literature. Our case, to our knowledge, is the only other reported case of malignant large cell calcifying Sertoli cell tumor with clinical and histopathological features related to aggressiveness, such as large tumor size, cellular pleomorphism, high mitotic rate, necrosis and aneuploid deoxyribonucleic acid. Such characteristics are not found in benign large cell calcifying Sertoli cell tumors.

Key words: Calcifying Sertoli cell tumor, Testis, Skip metastasis, Peutz-Jeghers syndrome

INTRODUCTION

Peutz–Jeghers syndrome (PJS), also known as hereditary intestinal polyposis syndrome, is an autosomal dominant genetically inherited disease characterized by the development of benign hamartomatous polyps in the gastrointestinal tract and hyperpigmented macules on the lips and oral mucosa (1). Multiple, round and oval, blue-black or dark brown macules measuring 1 to 12 mm occur typically on the lips, particularly the lower lip, and also on the mucous membrane of the gums, hard palate, genitalia and perianal region. The oral pigmentations are the first to appear, and thus play an important part in early diagnosis. Intra-orally, they are most frequently seen on the gingiva, hard palate and inside of the cheeks. The mucosa of the lower lip is almost invariably involved as well. They may also be present on the face, eye lids, hands and conjunctiva (2). Although, the pigmentations are commonly seen in early childhood, they may develop later in adulthood as well (3). Lesions on the oral mucosa remain constant throughout, while those present elsewhere often fade with time. Hamartomatous polyps in the gastrointestinal tract are

benign polyps with an extraordinarily low potential for malignancy. However, malignant changes have been reported to occur in 2-3% of patients (4). Apart from this, PJS is associated with various neoplasms outside the gastrointestinal tract such as testis, ovaries, breasts and eyes (5). Various reports exist confirming the association of PJS with ovarian tumors (5). However, the occurrence of Sertoli cell testicular tumors is uncommon. We highlight a man who presented with unilateral testicular tumor in association with PJS.

CASE SUMMARIES

A 44-year old male residing at Howrah, West Bengal, India, businessman by profession, presented with severe respiratory distress, high grade fever and productive cough for the past 3 months. The patient was apparently well 3 months before, when he first noticed rise of temperature and left sided chest pain along with cough and expectoration. Fever was high from the beginning(104-105^{0}F), intermittent in nature and not associated with chill or rigor that would relieve only after taking medications. Chest pain was pleuritic and localized in the left side. Cough was initially mild but it became severe within few days accompanying by thick, yellow and foul smell sputum about 50 ml per day. Afterwards, gradually increasing respiratory distress ensued, but it was not associated with hemoptysis. There was no history of weight loss during this period. He was admitted to a local hospital, where he received few intravenous antibiotics and was discharged almost asymptomatic with anti-tuberculosis drugs (ATD) on empirical basis. Thereafter, patient was apparently well for next two months. Meanwhile, he again suffered from high grade fever with chest pain over the same site along with productive cough. He was re-treated with some oral medications and subsequently fever subsided but other symptoms persisted, for which he was brought to our hospital for the first time and was immediately admitted.

Clinical examination revealed polycythemia, mild cyanosis and grade 2 clubbing (Figure 1). There was no significant palpable lymph node anywhere in the body. Though he was hemodynamically stable, tachypnea persisted for long. Respiratory system examination revealed woody dullness over left infrascapular region on percussion and bronchial breath sound along with coarse crackles over the same area on auscultation. Blood biochemical examination revealed Hb=18.9 mg/dl, TLC=20200 (Neu=85%, Lymph=12% ,Eos=1%), fasting blood sugar (FBS)=71 mg/dl, urea=23 mg/dl, creatinine=1.1 mg/dl with normal serum electrolytes and liver function tests. Chest X-ray revealed left sided consolidation with pleural reaction and right sided diffuse pneumonitic changes (Figure 2).Repeated pleural tap was unsuccessful. Thoracic HRCT was suggestive of consolidation at left mid zone with pleural effusion at the base of the left lung (Figure 3). CT guided fine needle aspiration from left sided pleural effusion showed blood elements, a few foam cells and mesothelial cells. No malignant cell was seen .He was treated again with higher dosage of intravenous antibiotics and ATDs was also administered concomitantly. He was discharged with ATDs and advised bronchoscopy, as his coughs persisted. Since he got some relief from dyspnea and chest pain, he refused to undergo bronchoscopy.

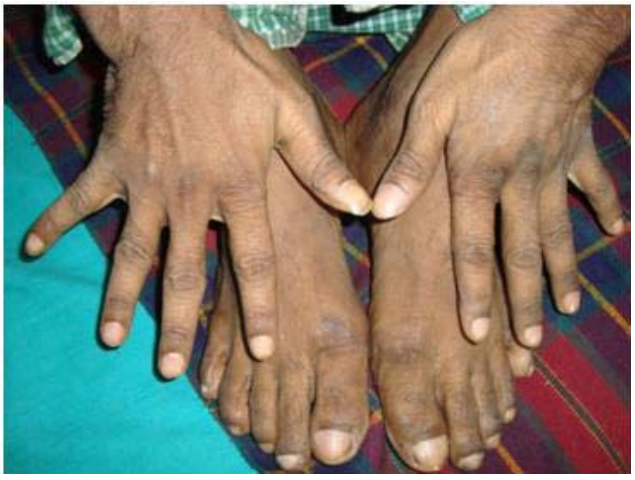

Figure 1. Showing Clubbing.

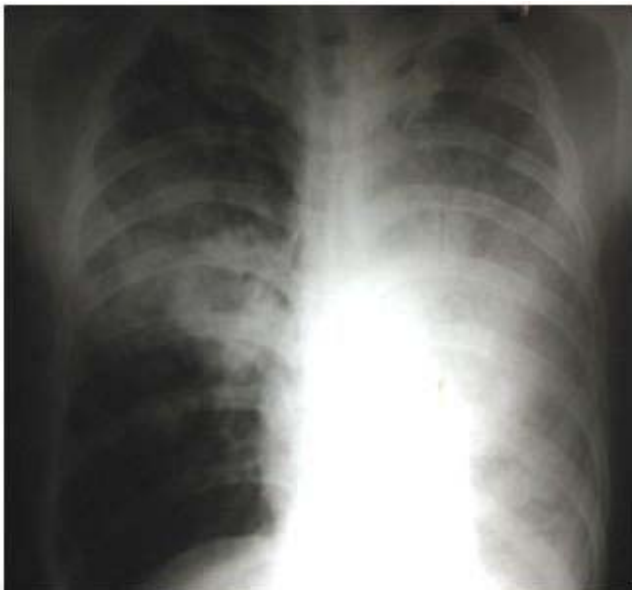

Figure 2. Chest X-Ray showing left sided consolidation with pleural reaction and right sided diffuse pneumonitic changes.

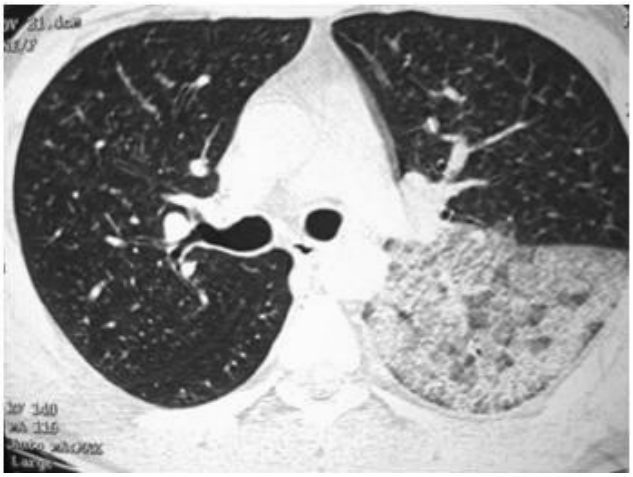

Figure 3. Thoracic HRCT showing consolidation at left mid zone with pleural collection in left base.

After an event free interval of 3 months he felt similar problem as in previous episodes. These symptoms were sudden onset and patient was rushed to the emergency department and admitted accordingly. Dyspnea was severe and fever was high, continuous and associated with chill. The amount of sputum was huge with whitish color and foul smell. On physical examination, cyanosis and clubbing were present with respiratory rate of 30/min, pulse rate of 110/min and BP of 110/80 mmHg. No lymph nodes were palpable throughout in the body .On respiratory system examination, trachea was central in position, chest movement was diminished in left side, breath sounds decreased in both sides (more at the left side), and coarse crepitation was present in both sides of chest. Other system examinations showed no abnormality except scrotal examination which revealed a hard mass involving right testis with loss of testicular sensation. Left testis was normal. He developed a new symptom, hyper-pigmented macules over the lower lip, margin of tongue and buccal mucosa. This time, his baseline investigations showed higher level of hemoglobin with other parameters being within normal range. Results of biochemical analysis revealed normal serum levels of thyroid stimulating hormone (TSH), free thyroxin (FT4), alpha fetoprotein, sex hormone binding globulin, testosterone and estradiol, assayed on two different occasions. The levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin and angiotensin converting enzyme did not reveal any abnormality. The 24-hour urinary steroid excretion was normal. The serum estrogen level was undetectable. Serum LDH was 1254 U/L(N<240 U/L),β-hCG was 1.71 mIUv/ml(normal adult male/normal adult non pregnant female-0.1-5.7). HIV-COMB test to detect HIV antibody was non reactive. Apart from routine investigations, bronchoscopy was performed and broncho-alveolar lavage (BAL) fluid was cultured and diagnosed as Klebsiella pneumonia. Culture was negative for tuberculosis in BACTEC media and cytology could not detect malignant cells. Keeping in mind the newly developed oral mucosal pigmentations, Barium meal x-ray and follow-through was performed which showed gastric dilatation with sub-optimal mucosal coating; no obvious gastric polyps were seen. Upper gastrointestinal endoscopy was also inconclusive. However, colonoscopy detected multiple polyps (Figure 4) which upon histopathological examination were proved to be of hamartomatous nature without any malignant character, confirming the diagnosis of PJS. There was no history of exposure to any drugs and no family history of PJS.

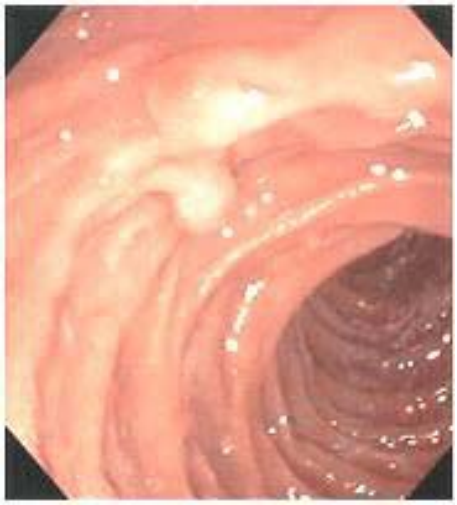

Figure 4. Colonoscopic view showing multiple polyps

Antibiotics were administered according to the drug sensitivity report. Chest X-ray was taken showing left sided non resolving pneumonia. He was treated with injectable piperacillin, tazobactam and gentamicin, and nebulisation with salbutamol. Abdominal Ultrasound was normal, but scrotal ultrasound revealed a large (10cm X 7.8 cm) mixed echogenic mass lesion involving the whole right testicular substance with dispersed necrotic areas suggestive of testicular malignancy. Left testis and epididymis were normal. High inguinal orchidectomy on right side was performed and histopathological examination of biopsy specimen showed large cell calcifying Sertoli cell tumor (Figure 5). Immunohistochemistry showed tumor cells expressing Inhibin, Calretinin and CD 56 and were immune negative for CK-7 and EMA. The tumor also stained positively for erythropoietin. Thus, a testicular tumor secreting ectopic erythropoietin explained the polycythemia in this patient. The aromatase activity was measured in the testicular biopsies and the levels detected were as follows: right testis, 1183 pmol/h/g protein and left testis 1358 pmol/h/g protein. These values were much higher than what is found in normal adult testis (33 pmol/h/g protein). Chest CT revealed variegated mass lesion and CT-guided FNA from lung lesion showed evidence suggestive of metastasis from testicular tumor. Abdominal CT revealed no obvious peri- or para-aortic lymphadenopathy (skip metastasis) and brain CT appeared to be normal.

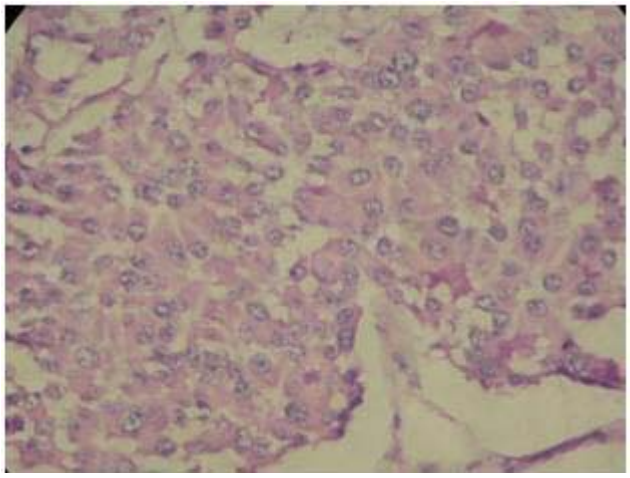

Figure 5. Histopathological examination of biopsy specimen of right testis showing large cell calcifying Sertoli cell tumor

The patient was put on a chemotherapy regimen comprising of bleomycin, etoposide and cisplatin. Though he tolerated the induction phase well, subsequently developed sepsis secondary to pancytopenia in the late consolidation phase and ultimately died despite all possible medical supportive therapy.

DISCUSSION

Large cell calcifying Sertoli cell tumor is not a common variant of Sertoli cell tumor since it represents less than 1 percent of all testicular neoplasms (6). Proppe and Scully first described the subtype, large cell calcifying Sertoli cell tumor in 1980 (7). Though the isolated form of the tumor is more common, it may be associated with genetic defects like Carney complex and Peutz-Jeghers syndrome. Forty-nine of these tumors have been described in the literature to date, with mean age of 21 yrs. (8). Among the 49 cases detected, 41 were benign and the remaining 8 were clinically malignant, with regional lymph node metastasis at the beginning or during follow-up (8).However, in our

report the tumor directly metastasized to the lungs without regional lymph node involvement in pelvis or abdomen, making it a unique feature. The likelihood of malignant behaviour can be evaluated with the help of different features. Malignant tumors are commonly found in an older population and tend to be larger like in this case (8). Kratzer et al. recommends that tumors be marked as malignant when they fulfil 2 or more of the following criteria: extra testicular involvement, size more than 4 cm, mitoses more than 3 per 10 high power fields, extensive nuclear atypia , necrosis, or lymphoreticular invasion (9). All patients with a diagnosis of malignant tumor developed retroperitoneal lymph node metastases, however we could not document it in our case. Many had hematogenous metastases to the bone, liver and lungs as well (9).

Macroscopically, the average diameter of this tumor is 2 cm. It might be multifocal, and bilateral in 1 out of 5 patients (10). These tumors are well delineated and show a white or tan granular cut surface. Microscopically, the tumor is composed of round to polygonal cells arranged in sheets with central calcification in the majority of patients (8). These cells have adequate and finely granular eosinophilic cytoplasm. The nuclei are round to oval in shape with prominent nucleoli and rarely mitotic figures. are noted (8). The stroma varies largely from myxoid to fibrous variety (11). The malignant cells are strongly positive for vimentin and S100, though cytokeratin is either negative in the majority of patients or only focally positive (11). Smooth and rough endoplasmic reticulum might be present in variable amounts. Charcot-Bottcher bodies and perinuclear bundles of filaments are rarely present (11).

The co-occurrence of ovarian sex cord tumors and PJS was reported to occur more frequently. Young et al. elaborated 74 cases of ovarian tumor of whom, 27 had associated PJS (5) .However, testicular tumors are very rarely reported in patients with PJS. To the best of our knowledge, our patient is the eight such case reported.

Cantu et al. (12) described a 6-year old boy having left testicular tumor of 7 mm diameter composed of tubules filled with Sertoli cells. The patient underwent orchidectomy; thereafter, the serum estrogen level came down to pre-pubertal level. The child remained well during follow-up for next 2 years.

Dubois et al. (13) reported a 3 year-old boy who presented with left testicular tumor. Orchidectomy was performed and histopathology report came to be ovoid lobulated mass replacing three fourth of the testis.

It has been considered that, 1.5% of childhood cancers are represented by testicular tumors. Embryonal carcinoma is the single most common testicular tumor in childhood. This malignant and rapidly growing tumor is characterized by elevated serum levels of alpha fetoprotein. Sertoli cell tumor in general occurs in all age groups of patients; 12% were known to have a malignant course among 128 cases of Sertoli cell tumor found in the literature (7). In many other cases, the evaluation of malignancy was incomplete due to inadequate follow-up. Only seven cases of testicular malignancy in association with PJS have been reported to date excluding ours. Though the incidence of PJS is equal in both sex groups, the occurrence of ovarian tumors far exceeds the testicular ones. Few cases of Sertoli cell tumor had evidence of virilization or in some cases precocious puberty (7).

It may also be appropriate to screen all patients with PJS for underlying testicular tumor in order to make an early diagnosis and to prevent unnecessary extensive investigations, particularly because Sertoli cell tumor might be associated with hormonal production. We want to highlight this case study because 1) Although Sertoli cell tumor of testis is common, malignancy is not a common association; 2) Malignant character without any intra abdominal lymphadenopathy or malignant deposit with direct metastasis to lung is a rare clinical association; 3) This is the eight case reported so far disclosing the association between Peutz-Jeghers syndrome with testicular tumor. Clinicians should be aware of this clinical situation during planning the definitive management.

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